

Amebiasis

*Mary K. Klassen-Fischer,
Douglas J. Wear, and Ronald C. Neafie*

Introduction

Definition

Amebiasis is invasion of human tissues by the protozoon *Entamoeba histolytica*. Infection begins when trophozoites of *E. histolytica* invade the colonic mucosa. The infection may remain localized and be minimal for years, or it may extend to the liver and other organs. What was once thought to be a single species based on morphology is now known to be three genetically distinct species: *Entamoeba histolytica* (pathogen), *Entamoeba dispar* (commensal),¹ and *Entamoeba moshkovskii* (commensal).² The free-living amebas that cause meningoencephalitis are discussed in Chapter 9, those infecting other sites are included in this chapter.

Synonyms

Amebic dysentery, amebic colitis, amoebiasis (British spelling)

General Considerations

Hippocrates noticed that dysenteries are especially bad “when they are set in with fever, [intestinal] discharges of a mixed character, or with inflammation of the liver”. Two thousand years later in 1875, Lösch described trophozoites, which he named “Amoeba coli”, in the stool and colonic ulcers in a Russian farmer.³ Schaudinn distinguished *Entamoeba histolytica* from *Entamoeba coli* in 1903. In 1925, Brumpt proposed

that two morphologically identical species of *Entamoeba*, *Entamoeba dysenteriae* (pathogenic) and *E. dispar* (non-pathogenic), can infect humans. During the 1933 Chicago World’s Fair, faulty plumbing in a hotel resulted in 1,704 cases of amebic dysentery.⁴

Epidemiology

Amebiasis is the third leading cause of death from parasitic disease worldwide (behind malaria and schistosomiasis), resulting in 40 to 100 thousand deaths annually.^{1,5} It is most prevalent in regions where human waste is used as fertilizer. Severity of amebiasis varies greatly among patients and geographic areas. Many people are asymptomatic carriers, and others have sudden severe infections that progress steadily to death.^{6,7} There is a spectrum of disease patterns between these extremes.⁸ For unknown reasons, some urban populations (particularly in Mexico City, Mexico; Medellín, Colombia; Durban, South Africa; and Kuala Lumpur, Malaysia)⁹ are predisposed to severe amebiasis, causing complications and death. Most cases in the United States occur in immigrants from endemic areas and in the states that border Mexico. Some possible contributing factors to the initiation of infection and promotion of severe disease include poor nutrition, tropical climate, decreased host immunocompetence, stress, altered colonic bacterial flora, excessive alcohol ingestion, and heredity. The disease has re-emerged in previously quiescent areas.^{1,10}

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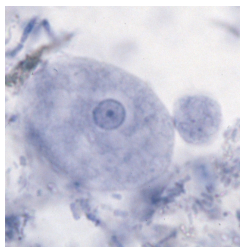


Figure 8.1
Entamoeba histolytica trophozoite in fecal smear is 24µm in diameter and contains a single, spherical, 5µm diameter nucleus with a discrete, round, centrally placed karyosome. The peripheral chromatin lining the nuclear membrane is uniform. Iron hematoxylin x800

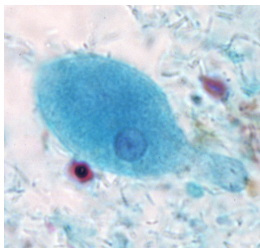


Figure 8.2
Entamoeba histolytica trophozoite in fecal smear producing pseudopodia. This trophozoite is 35µm long and has a 5µm diameter, spherical, nucleus. The karyosome is centrally placed. The cytoplasm has a finely granular, green appearance. Trichrome x875

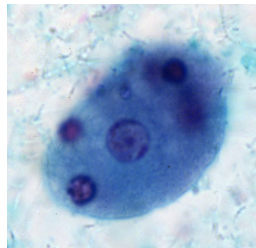


Figure 8.3
Entamoeba histolytica trophozoite in fecal smear with a large 6µm diameter nucleus and several ingested erythrocytes. The nucleus has irregular peripheral chromatin and a centrally placed karyosome. Trichrome x1000

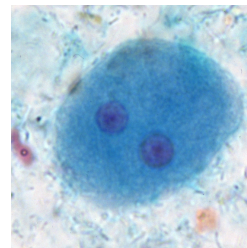


Figure 8.4
Entamoeba histolytica trophozoite in fecal smear demonstrating rare double nuclei. This trophozoite is 29µm long and the nuclei are 5µm in diameter. Trichrome x875

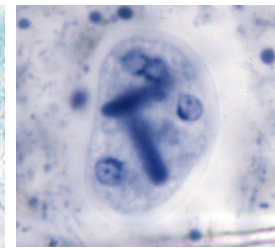


Figure 8.5
Entamoeba histolytica mature cyst with 4 nuclei and chromatoid bodies in fecal smear and surrounded by halo-like space. The cyst is 19µm long and the nuclei are 3µm in diameter. The nucleus has irregular peripheral chromatin and both centric and eccentric karyosomes are observed. Iron hematoxylin x850

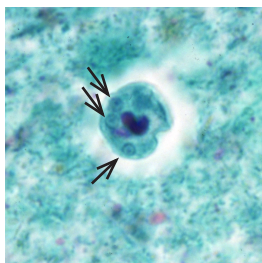


Figure 8.6

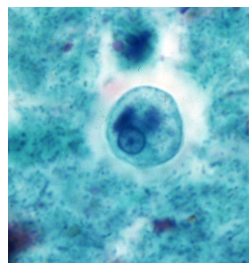


Figure 8.7

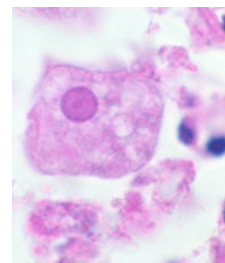


Figure 8.8

Figure 8.6

Mature *Entamoeba histolytica* cyst in fecal smear. Three of the four nuclei (arrows) are visible as are the red-staining chromatoid bodies. Trichrome x900

Figure 8.7

Entamoeba histolytica precyst in fecal smear with a single nucleus. Cyst is 12µm in diameter and the nucleus is 4µm in diameter. The peripheral chromatin is uniform and the karyosome is centrally placed. Trichrome x875

Figure 8.8

Entamoeba histolytica trophozoite in lung abscess. The ameba cytoplasm is eosinophilic, coarse, and vacuolated. The nucleus is 5µm in diameter and there is peripheral chromatin lining the nuclear membrane. The tiny karyosome is centrally placed. H&E x930

Infectious Agent

Morphologic Description

Entamoeba histolytica occurs in humans in two forms: trophozoites and cysts. Trophozoites are in both stool and tissue, but cysts are only in stool. Although cysts form in the lumen of the intestinal tract, they are not observed in biopsy specimens. Stool specimens that contain only trophozoites are usually from patients with acute symptoms.

Entamoeba histolytica trophozoites in stool specimens range from 10µm to 60µm (Fig 8.1). Living trophozoites exhibit progressive, sometimes explosive, motility with extrusion of hyaline, finger-like pseudopodia (Fig 8.2). In unstained preparations, the single nucleus is not visible. In stained fecal smears, trophozoites are spherical to elongate and usually range from 12µm to 30µm in diameter. With iron-hematoxylin staining, amebae take on a grayish to black color, blending in with the background (Fig 8.1). The nucleus is spherical and varies from 3.5µm to 6.0µm in diameter. The peripheral chromatin lining the inner surface of the nuclear membrane may be even or uneven (Figs 8.1 & 8.3). The nucleus has a small, compact karyosome (nucleolus) that is usually centrally

located, but may occasionally be eccentric. The cytoplasm of the ameba is usually finely granular and green to purple with trichrome staining (Figs 8.2 to 8.4). Amebic trophozoites with pseudopodia are frequently seen as are amebae with ingested erythrocytes (Fig 8.3).

Trophozoites of *E. histolytica* usually do not contain bacteria or debris. Rarely, a trophozoite may contain two nuclei (Fig 8.4). Delays in fixation may cause vacuoles to develop in the cytoplasm and produce variations in nuclear morphology. In trophozoites undergoing degeneration, the nucleus is usually the first structure to undergo changes including fragmentation of the karyosome or alteration of the peripheral chromatin.

Entamoeba histolytica cysts in stool specimens are usually spherical and range from 9µm to 20µm in diameter, although most are 12µm to 15µm. The fixation process may cause cysts to shrink resulting in a clear unstained halo-like space, an appearance that is useful in detecting cysts while scanning the fecal smear (Fig 8.5). The mature cyst contains 4 nuclei; rarely 8 (Fig 8.5). It is often difficult to see all 4 nuclei in the same focal plane (Fig 8.6). Immature cysts or precysts contain one or two nuclei (Fig 8.7). The

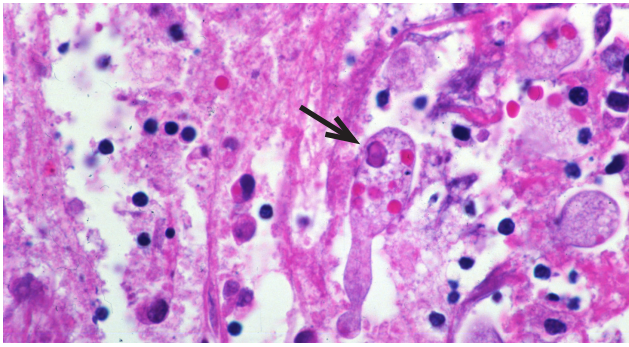


Figure 8.9
Entamoeba histolytica trophozoite with pseudopodium in colonic ulcer. The ameba has a single nucleus (arrow) and has engulfed several erythrocytes. H&E x480

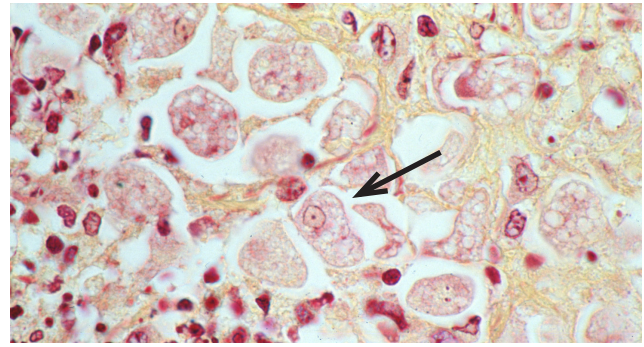


Figure 8.10
Entamoeba histolytica trophozoites in colonic ulcer demonstrating nucleus with tiny, centrally placed karyosome (arrow). B&H x480

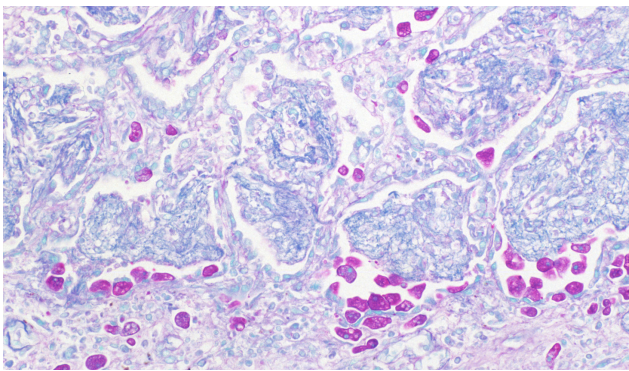


Figure 8.11
Entamoeba histolytica trophozoites are bright red and are easily distinguished in this PAS stained section of lung. PAS x120

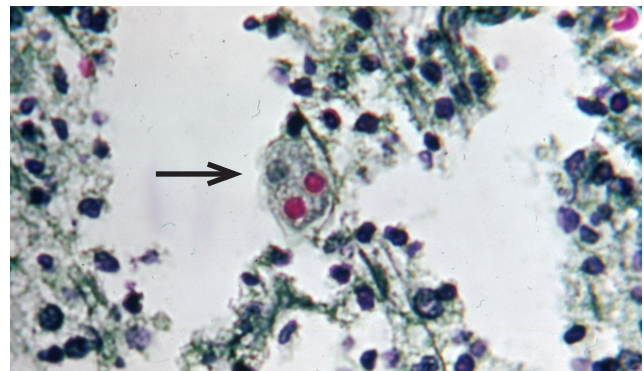


Figure 8.12
Entamoeba histolytica trophozoite in lumen of appendix. Note gray nucleus (arrow) and two bright red engulfed erythrocytes. Gridley ameba x710

nuclei of cysts vary from 2µm to 4µm, and they are smaller than those of trophozoites, but otherwise morphologically similar. The nuclei of immature cysts are generally larger than those in mature cysts.

Glycogen in mature cysts is usually diffuse, but may be concentrated into a discrete mass in young cysts. Chromatoid bodies, which are ribosomal assemblies, appear as highly refractile, cigar-shaped bars that are bright red with trichrome staining and gray to black with iron hematoxylin staining (Figs 8.5 to 8.7).

In biopsy or autopsy specimens *E. histolytica* trophozoites rarely exceed 35µm in greatest dimension. They are readily visible in H&E stained sections of paraffin embedded tissue and this stain best illustrates their morphologic features (Figs 8.8 & 8.9). They are well demarcated from other surrounding cells and tissue. The nucleus is usually 4µm to 5µm in diameter, has peripheral chromatin lining the nuclear membrane, and contains a tiny centrally placed karyosome (Fig 8.8). Frequently, the nucleus is not observed due to the plane of section. The tiny karyosome is usually difficult to see and is often absent. The Brown-Hopps tissue gram stain sometimes accentuates the karyosome (Fig 8.10).

The cytoplasm of *E. histolytica* trophozoites is eosinophilic, coarse, and vacuolated. Trophozoites occasionally develop pseudopodia and often engulf erythrocytes (Fig 8.9). The amebic cytoplasm usually contains abundant glycogen that stains deeply with PAS, which may help in locating trophozoites (Fig 8.11). However, the PAS stain frequently obscures the morphologic features of the nucleus and sometimes will also deeply stain histiocytes. For these reasons, we prefer the H&E stain for studying *E. histolytica* in tissue sections. The Gridley ameba stain is useful

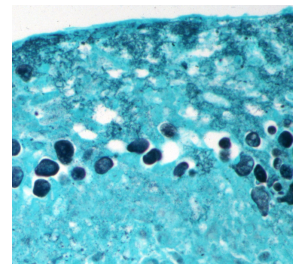


Figure 8.13
Entamoeba histolytica trophozoites in ulcerated cervix. GMS x190

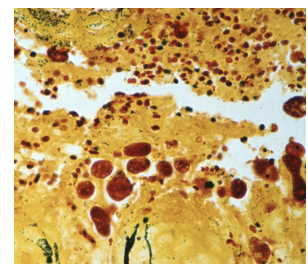


Figure 8.14
Entamoeba histolytica trophozoites in ulcerated foreskin. WS x190

in demonstrating engulfed erythrocytes (Fig 8.12). Other stains that maybe helpful in demonstrating trophozoites includes GMS and WS (Figs 8.13 & 8.14).

Life Cycle and Transmission

Although there are 5 stages of the parasite: trophozoite, precyst, cyst, metacyst, and metacystic trophozoite, the life cycle is rather simple (Fig 8.15). Humans usually become infected by ingesting cysts of *E. histolytica* in fecally contaminated water or food. More unusual modes of transmission include oral and anal sex and exposure to contaminated enema apparatus. The ingested cyst passes through the stomach into the small intestine where excystation occurs resulting in the emergence of a 4 nucleated metacyst. The metacyst cytoplasm divides almost immediately resulting in 4 small metacystic trophozoites. The metacystic trophozoites quickly feed and grow into normal-sized trophozoites that pass with the fecal stream into the cecum where colonization occurs. Trophozoites are highly motile and reproduce by binary fission resulting in large numbers of organisms, some of which may invade the intestinal mucosa. Factors controlling invasion may include parasite “quorum sensing,” interactions of amebae with colonic bacterial flora, and innate and acquired immune responses of the host.¹¹ In some patients, trophozoites directly extend or by hematogenous spread involve distant organs such as liver, lung, and brain (Fig 8.16). The reproduction of trophozoites has no sexual cycle. The overall population of *E. histolytica* appears to be clonal.¹² Trophozoites ingest erythrocytes, bacteria and food particles. Under certain undefined conditions, possibly triggered by the parasite’s surface galactase/N-acetylgalactosamine (GAL/GALNAC) specific lectin, aggregates of trophozoites in the mucin layer differentiate into precysts and then into cysts that are passed in the stool.¹³ The precyst is usually spherical, has a thin wall, and single nucleus. The precyst nucleus undergoes two divisions resulting in the quadrinucleated cyst. Stool specimens may contain trophozoites and uninucleate, binucleate, and quadrinucleate cysts. Trophozoites cannot survive outside the host, but cysts may survive for days.

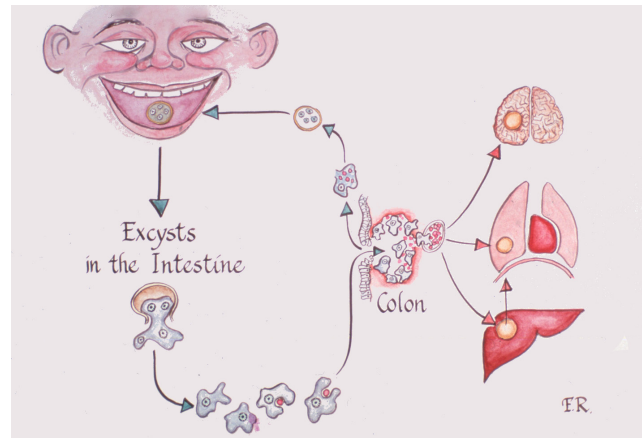


Figure 8.15

Life cycle of *Entamoeba histolytica*. Humans are infected by ingesting cysts that transform into metacystic trophozoites that colonize the colonic mucosa. In some patients, amebae disseminate to distant organs including liver, lung, and brain.

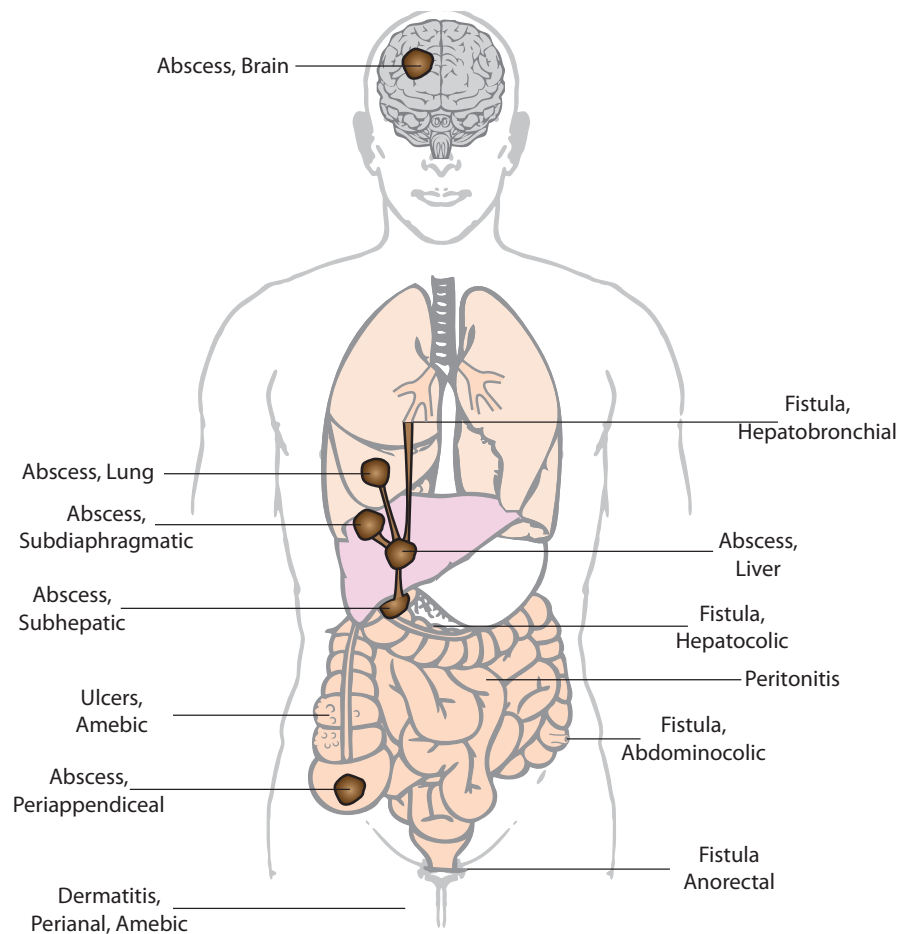


Figure 8.16

Schematic representation of complications of amebiasis.

Clinical Features and Pathogenesis

The specific name “histolytica” refers to the appearance of a clear zone surrounding trophozoites in tissue sections, presumed to be due to parasite toxins or enzymes.¹ The clear zone may be an artifact caused by shrinkage during fixation. Studies by electron microscopy, however, reveal degeneration of epithelial cells as trophozoites approach, supporting the theory that trophozoites elaborate cytolytic substances. Amoebapores, pore-forming peptides, and proteinases secreted by the parasite cleave immunoglobulin and complement components, and may contribute to colonic cell lysis.^{5,14} When the parasite Gal/GalNAc-specific lectin attaches to host cell intestinal surface mucin glycoproteins, commensal infection results and leads to host cell apoptosis.¹⁵ The Gal/GalNAc-specific lectin prevents assembly of complement C5b-C9 complex, contributing to evasion of the immune response.¹⁶ Invasion by trophozoites causes secretion of cytokines from host cells, leading to an acute inflammatory response. Recently PATMK, a member of the transmembrane kinase family was found to be a key in human erythrocyte phagocytosis.¹⁷

The spectrum of amebiasis includes a range of clinical presentations including asymptomatic carriage, diarrhea and liver abscess and may be related to variations in host factors and the parasite genome.^{18,19} Patients typically present with a several-week history of gradually increasing cramping lower abdominal pain, weight loss, and recurring bouts of watery, mucoid or bloody diarrhea.¹¹ The insidious onset, variable signs and symptoms and frequent absence of fever or grossly bloody stool make diagnosis difficult. Other symptoms may include malodorous flatus, intermittent constipation, nausea, vomiting, right-sided cramps, fatigability, loss of appetite and tenesmus. Stools may increase to 25 per day, with weakness and prostration. Any portion of the abdomen may be tender, but maximum tenderness is over the portion of the colon that is most severely involved. Amebic colitis is more severe in patients who are very young, old or receiving corticosteroids.¹¹ Sometimes the clinical picture is acute, suggesting appendicitis, cholecystitis, intestinal obstruction, diverticulitis, a ruptured viscus, pneumonia, or lung abscess. Stools are occult heme-positive, even if no blood is seen. Rectal bleeding without diarrhea may be seen, especially in children. There may be fecal leukocytosis, although to a lesser degree than that in shigellosis. Circulating leukocytes may rise to 20,000 mm³.

Amebic colitis often persists for weeks, months, or years, and, during intervals between acute attacks, patients may have recurring cramps and soft loose stools, especially after meals. If untreated, those with severe infections become emaciated and anemic. Chronic intestinal amebiasis without dysentery can resemble ulcerative colitis clinically and

result in inappropriate treatment with corticosteroids.⁵

The differential diagnosis of diarrhea with hematochezia includes *Shigella*, *Salmonella*, *Campylobacter*, and enteroinvasive and enterohemorrhagic *Escherichia coli* infection. Noninfectious causes include inflammatory bowel disease, ischemic colitis, diverticulitis, and arteriovenous malformation.⁵

Unusual manifestations of amebic colitis include acute necrotizing colitis, toxic megacolon, ameboma, perianal ulceration with fistula formation and amebic appendicitis.¹¹ Fulminant disease is increased in pregnant women, immunocompromised patients and those receiving steroids. Associations with diabetes and alcohol use have been reported. Acute necrotizing colitis is rare (occurring in less than 0.5% of cases) and is associated with a mortality rate of more than 40%.²⁰ Patients with acute necrotizing colitis typically appear very ill, with fever, bloody mucoid diarrhea, abdominal pain with rebound tenderness, and other signs of peritoneal irritation. Surgical intervention is indicated if there is bowel perforation or if the patient has no response to antiamebic therapy.

Toxic megacolon is rare (occurring in approximately 0.5% of cases) and is typically associated with corticosteroids use.¹¹ Early recognition and surgical intervention are important, since patients with toxic megacolon usually have no response to antiamebic therapy alone and peritonitis from perforation may occur.

Ameboma (also called amebic pseudotumor) of the colon occurs in 1 to 5% of patients and is a result of annular inflammatory thickening usually in the wall of the cecum or ascending colon. Ameboma may mimic carcinoma by location, symptoms, x-ray examination, and gross appearance.²¹

Extraintestinal complications of amebiasis include hepatic, subdiaphragmatic, periappendiceal, and subhepatic abscesses; perianal amebic dermatitis; and hepatobronchial, hepatocolic, abdominocolic or anorectal fistulas (Fig 8.16). Complications of amebic liver abscess may arise from rupture of the abscess with perforation and peritonitis and extension into the peritoneum, pleural cavity or pericardium.²² Extrahepatic amebic abscesses, presumably from hematogenous spread, have occurred in lung, skin and, very rarely, brain.

Amebic liver abscess (Fig 8.17a) is up to 20 times as common in men as in women and rare in children.¹¹ The Zulu word for it is “isigwebedhla” meaning “disease of strong young men”.¹ Most patients present with symptoms that develop relatively slowly over 2 to 4 weeks, including fever, cough, and constant dull, aching abdominal pain in the right upper quadrant or epigastrium. Usually there is a single abscess in the right lobe. Involvement of the diaphragmatic surface of the liver may lead to right-sided pleural pain or referred shoulder pain. Gastrointestinal symptoms occur in only 10 to 35% of patients, and stool microscopy is often negative for parasites. Hepatomegaly with point tenderness

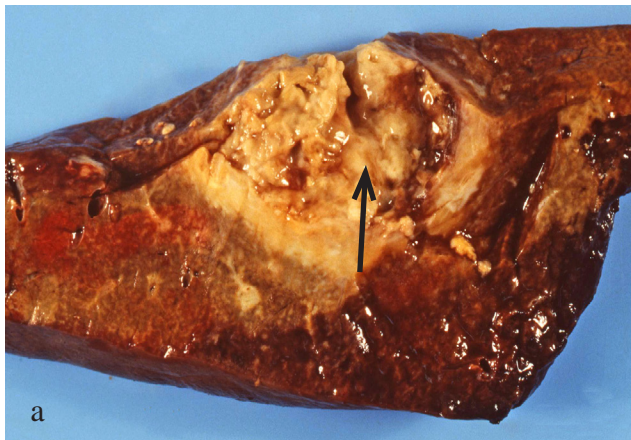


Figure 8.17 a,b

44-year-old man with colonic amebiasis complicated by an (a) amebic hepatic abscess (arrow); b. Contrast-enhanced CT shows mural thickening of the transverse colon (white arrow) and peripherally located hepatic abscess (black arrow) that is characterized by central fluid attenuation, an enhancing wall, and a peripheral rim of edema.

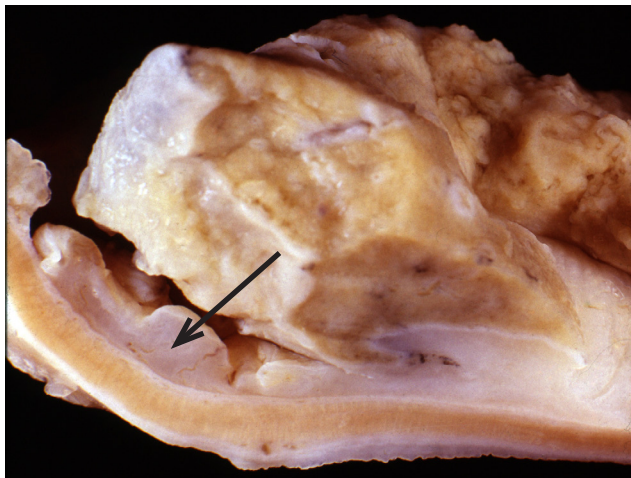


Figure 8.18

Amebiasis of lung and pleura (arrow) with attached diaphragm.



Figure 8.19

Cutaneous amebiasis involving anus and perianal skin. This is an extension from amebiasis of the rectum and has a cauliflower appearance caused by epithelial hyperplasia. Clinically, this appearance is easily mistaken for squamous cell carcinoma.

over the liver, below the ribs, or in the intercostal spaces is typical. Laboratory studies in patients with amebic liver abscess may reveal a mild to moderate leukocytosis and anemia.¹¹ Patients with acute amebic liver abscess tend to have a normal alkaline phosphatase level and elevated alanine aminotransferase level; the opposite is true of patients with chronic disease. Ultrasonography, abdominal computed tomography and magnetic resonance imaging are excellent for detecting amebic liver abscess (Fig 8.17b) but are not specific. The differential diagnosis includes bacterial abscess, necrotic hepatocellular carcinoma, and echinococcal cyst.¹¹ Compared to patients with bacterial liver abscesses, patients with amebic liver abscess are more likely to be male, younger than 50 years-old, immigrants from or travelers to an endemic area, and less likely to have jaundice, biliary disease or diabetes mellitus.

The lung is the second most common extraintestinal amebiasis after the liver. Infection usually spreads to the lungs through the diaphragm by extension of an amebic liver abscess. Pulmonary amebiasis (Figs 8.8 & 8.18) without liver involvement occurs sporadically due to hematogenous spread from the colon.^{23,24} The sputum may occasionally contain trophozoites.²⁴ Pericardial amebiasis is rare and usually due to extension from an amebic abscess of the left lobe of the liver, sometimes from the right lobe of the liver, and rarely from the lungs or pleura. Pericardiocentesis usually confirms the diagnosis and improves the patient's condition.²⁵

The skin may be involved by: (1) extension of rectal amebiasis to anus (Fig 8.19), perianal skin and vulva, (2) extension of a liver abscess to the skin of the abdominal wall or flank, or (3) infection of the penile skin (Fig 8.14) from



Figure 8.20

African patient with a 6 cm ulcer of the abdomen. Thick grayish pus containing many *Entamoeba histolytica* trophozoites drained from the ulcer, secondary to an amebic liver abscess.

anal intercourse. Primary cutaneous amebiasis is extremely rare.²⁶⁻²⁸ The initially small well-circumscribed ulcers may extend rapidly (Fig 8.20). They are acutely tender and malodorous with a gray-white necrotic base. In the anogenital area, epithelial hyperplasia causes a thickened cauliflower-like surface appearance that mimics carcinoma (Figs 8.19 & 8.21).

Patients with HIV infection are not at increased risk for amebic colitis. However, an increased incidence of amebic liver abscess among these patients has been reported which suggests that HIV infected patients are more susceptible to invasive disease.²⁵ *Entamoeba dispar* causes no signs of disease or mucosal invasion even in patients with AIDS.¹

Pathologic Features

Infection begins as small foci of superficial necrosis in the colonic mucosa. These foci progress to form ulcers. Some ulcers remain small and discrete; others expand or become confluent to form broad geographic patterns (Fig 8.22). Amebic ulcers are usually limited to one region, but may be disseminated throughout the colon. When limited, the cecum is the most common site involved. Less com-



Figure 8.23

Colon from adult male Ugandan with fatal amebiasis. The patient was thought to have a plasmacytoma and was treated with corticosteroids and other chemotherapeutic agents. The entire colon is studded with small, confluent ulcers, all covered with a heaped up gray exudates.



Figure 8.21

49-year-old man admitted for cardiac failure found to have an anal lesion consistent with carcinoma with metastasis to the lung. At autopsy there were extensive amebic ulcerations of the colon extending to the rectum, amebic hepatitis, but no pulmonary amebiasis.

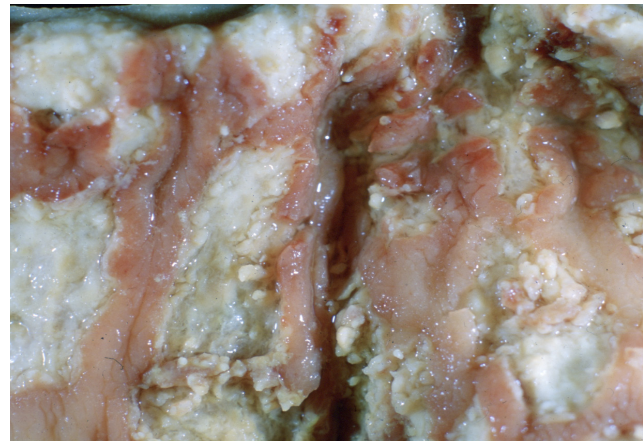


Figure 8.22

Colonic amebiasis in a 40 year-old woman from Pennsylvania who recently returned from a trip to Mexico. The ulcers are confluent and filled with exudates. She had chronic diarrhea, thought to have had ulcerative colitis, and was treated with corticosteroids. Ironically, 3 stool specimens were negative for ameba.

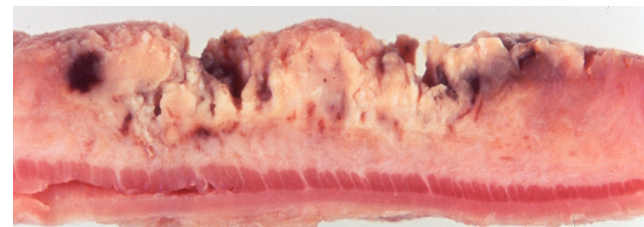


Figure 8.24

A vertical section of the specimen shown in Figure 8.23. The ulcer on the left has penetrated the submucosa but not the muscularis.

monly, ulcers are limited to the ascending colon, descending colon, or transverse colon. Rarely, there are amebic ulcers in the ileum near the ileocecal junction. The typical amebic ulcer is flask-shaped, undermined and sharply defined without ragged edges (Figs 8.23 & 8.24). The crater contains heaped up gray necrotic tissue. Sometimes, the exudate raises the undermined mucosa. Mucus may coat the mucosa between ulcers.

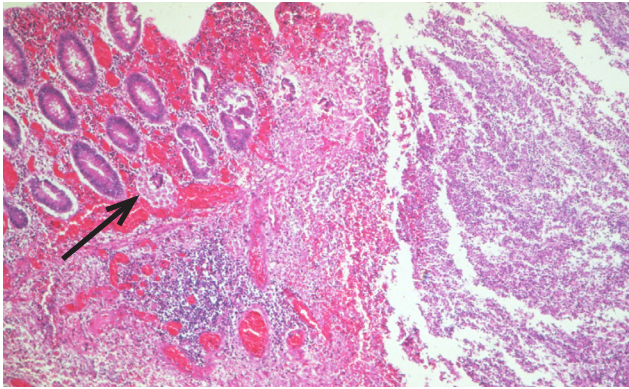


Figure 8.25
Ulcerated colon with destruction of the entire thickness of the mucosa. Note congested lamina propria and cluster of trophozoites (arrow). H&E x40

Microscopic examination can reveal a wide range of histopathological findings including diffusely inflamed mucosa, necrosis, acute inflammatory exudate, and ulceration that can extend through the muscularis mucosa into the submucosa (Figs 8.25 & 8.26).²⁹ The ulcer crater is comprised of fibrin, cellular debris, and trophozoites (Fig 8.27). Trophozoites may also be seen on the surface, in any layer of the colon and rarely in blood vessels. A narrow margin at the edge of the ulcer retains a faint outline of previously viable structures, suggesting that the necrosis may be partly ischemic (Fig 8.28). Early, there is little inflammatory response, but, as ulcers widen, neutrophils, lymphocytes, histiocytes, plasma cells, and sometimes eosinophils, accumulate in the crater and in the viable tissues around it. In well-established ulcers, inflammation may be minimal (Figs 8.29 & 8.30).³⁰

The typical histologic pattern is that of chronic crypt destructive colitis with mononuclear inflammatory cells extending into the deep lamina propria and crypt architectural distortion and branching (Fig 8.31).³¹ This pattern is not specific and similar to that seen in other conditions including: idiopathic chronic inflammatory bowel disease, common enteric bacteria infections (*Campylobacter*, *Shigella*, *Aeromonas*, and *Yersinia*), sexually transmitted diseases (syphilis and chlamydiosis), tuberculosis, fungal infections (histoplasmosis, cryptococcosis, coccidioidomycosis and candidiasis), and chronic nonsteroidal anti-inflammatory drugs use.

Grossly, amebomas are firm, well-defined enlargements of the colon wall. Like some carcinomas of the colon, they tend to cause a “napkin ring” constriction. Microscopically, amebomas are comprised of varying amounts of granulation tissue, fibrosis, chronic inflammatory cells, and clusters of trophozoites that usually concentrate in the submucosa near small points of ulceration (Figs 8.32 & 8.33).

Hepatic amebic abscesses may become very large, sometimes destroying an entire lobe (Fig 8.34). They contain

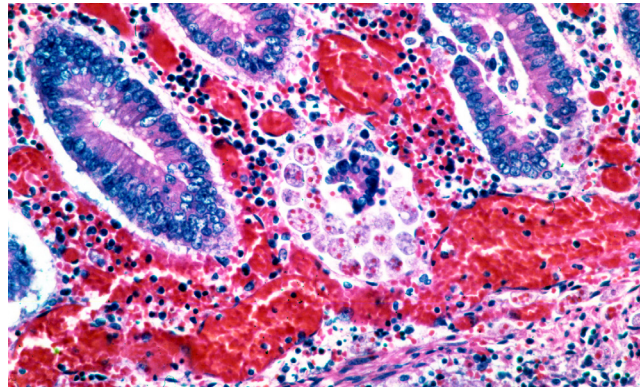


Figure 8.26
Higher magnification of trophozoites in Figure 8.25. Most have ingested several erythrocytes. H&E x180

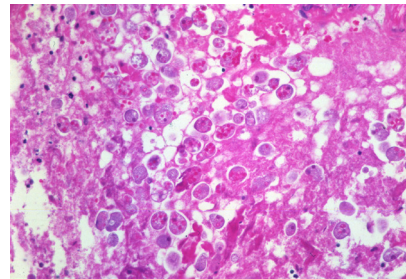


Figure 8.27
Ulcerated colon may contain massive numbers of trophozoites. H&E x110

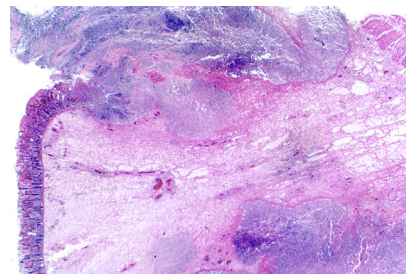


Figure 8.28
Narrow margin of ischemic type necrosis at the edge of ulcer. H&E x4.4

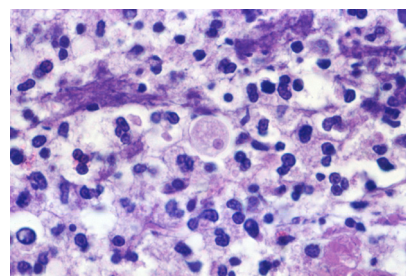


Figure 8.29
Neutrophils, lymphocytes, histiocytes and plasma cells join amebae in ulcer's crater. H&E x450

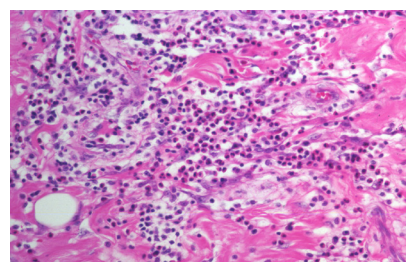


Figure 8.30
Amebic colitis in AIDS patient with massive tissue eosinophilia. H&E x110

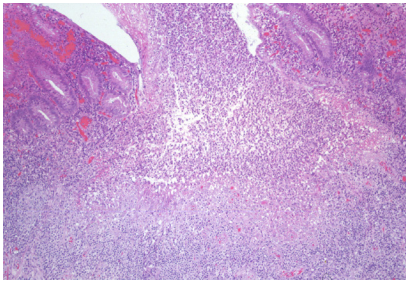


Figure 8.31
Typical flask-shaped ulcer in amebic appendicitis. H&E x40

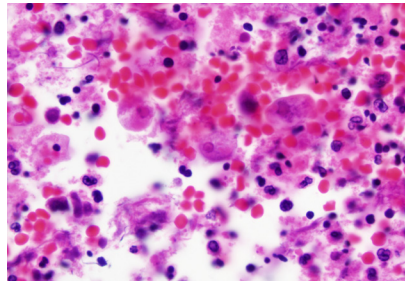


Figure 8.32
Ameboma with trophozoites in area of acute inflammation and congestion in colon. H&E x250

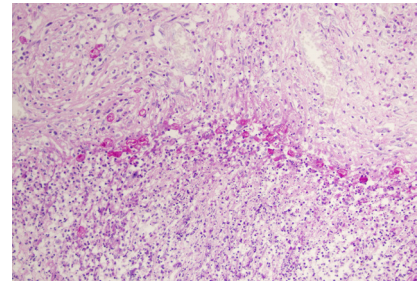


Figure 8.33
Ameboma with trophozoites lined up along border of necrotic and more viable tissue in wall of colon. H&E x40

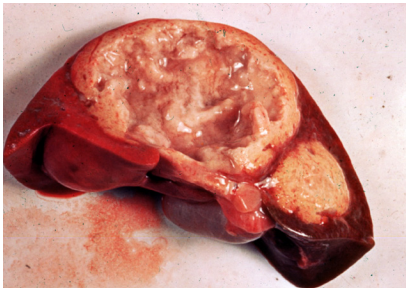


Figure 8.34
This large hepatic abscess has destroyed most of the right lobe and a large portion of the left lobe.

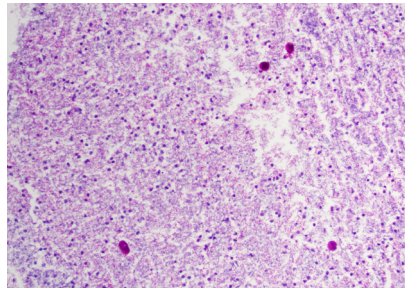


Figure 8.35
Liquified center of hepatic abscess is amorphous and necrotic with scattered trophozoites. PAS x40

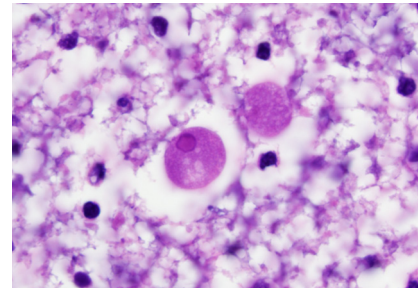


Figure 8.36
Viable trophozoites in liquid center of hepatic abscess that lacks neutrophils. H&E x480

yellow or gray, opaque liquid material. The wall is shaggy and fibrinous. Microscopically, the wall contains abundant fibrin. Trophozoites may be abundant or rare and are often clustered in the fibrin near viable hepatic tissue (Figs 8.35 & 8.36). The liquified center is amorphous and necrotic, but does not contain neutrophilic leukocytes as the term “abscess” suggests. The surrounding liver is edematous and may be infiltrated by mixed chronic inflammatory cells. Inflammation surrounding well-established liver abscesses is minimal, given the degree of tissue damage.³⁰

In a reported case of fallopian tube amebiasis, microscopic examination showed a poorly formed granuloma composed of large macrophages with many trophozoites in the lumen.³²

In cutaneous amebiasis, there is benign epithelial hyperplasia that may have a cauliflower appearance grossly, mimicking squamous cell carcinoma (Fig 8.19). Microscopically, there is papillary acanthosis and ulceration of the epithelium (Fig 8.37).³³ The dermis is hyperemic to necrotic and infiltrated by lymphocytes, plasma cells, and, sometimes, eosinophils. Trophozoites are concentrated over the points of ulcer-

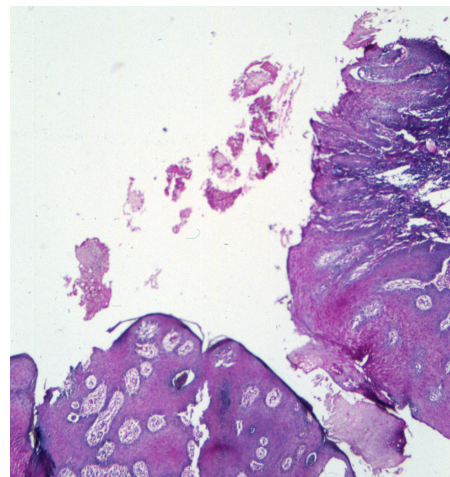


Figure 8.37
Amebiasis of anal skin with papillary acanthosis and ulceration. PAS x66

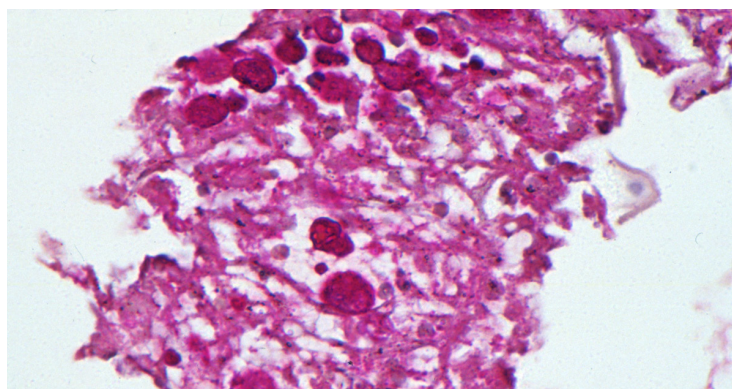


Figure 8.38
Clusters of trophozoites concentrated in exudates of ulcer seen in Fig 8.37. PAS x1200

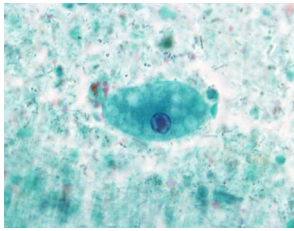


Figure 8.39
Entamoeba coli trophozoite (32µm diameter) in feces, note large karyosome and vacuoles. Trichrome x350

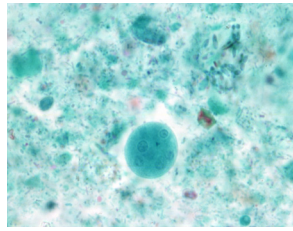


Figure 8.40
Entamoeba coli cyst (17µm diameter) in feces, note 5 nuclei. Trichrome x350

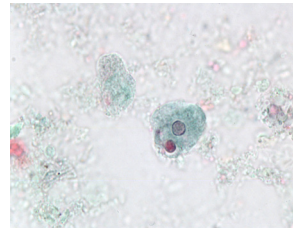


Figure 8.41
Entamoeba polecki trophozoite (18µm diameter) in fecal smear with ingested RBC and one nucleus. Trichrome x350

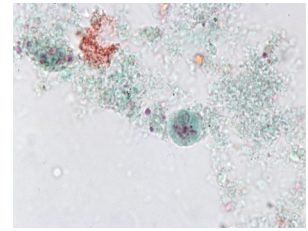


Figure 8.42
Entamoeba polecki cyst (11µm diameter) in fecal smear with chromatoid body. Trichrome x350

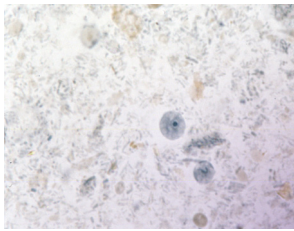


Figure 8.43
Endolimax nana trophozoite (8µm diameter) with large karyosome in fecal smear. Trichrome x350

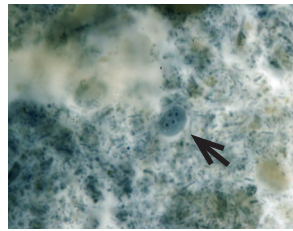


Figure 8.44
Endolimax nana cyst (10µm diameter) with 4 nuclei in fecal smear (arrow). Trichrome x350

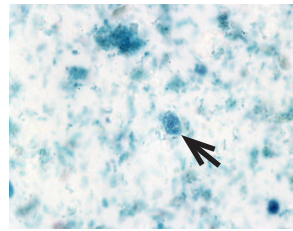


Figure 8.45
Entamoeba hartmanni trophozoite (8µm diameter) with one central nucleus (arrow). Trichrome x350

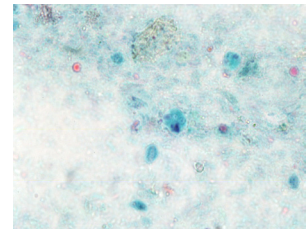


Figure 8.46
Entamoeba hartmanni cyst (7µm diameter) with two nuclei. Trichrome x350

ation in adjacent epidermis and in the superficial layers of the ulcer (Fig 8.38).

Diagnosis

Patients presenting with a history of diarrhea or dysentery must first be evaluated to separate cases of invasive diarrhea from cases of secretory diarrhea. Initial diagnostic evaluation includes fecal testing for lactoferrin, leucocytes or occult blood.

Intestinal amebiasis is often diagnosed by identifying cysts or motile trophozoites on a saline wet mount of stool. Only rare patients with symptomatic amebic colitis pass cysts without trophozoites. This method has low sensitivity, and false positive results occur in the presence of nonpathogenic species *E. dispar* or *E. moshkovskii*, which are microscopically identical to *E. histolytica*.^{5,34} The presence of erythrophagocytosis by trophozoites in the stool of a patient with bloody diarrhea is considered diagnostic of *E. histolytica* infection. *Entamoeba dispar* rarely contains red blood cells; therefore, in the absence of erythrophagocytosis, *E. dispar* cannot be excluded and bacterial dysentery should be considered. The differential diagnosis of *E. histolytica* in stool, cytologic specimens and tissue sections includes *Entamoeba coli*, *Entamoeba polecki*, *Endolimax nana*, *Entamoeba hartmanni*, *Entamoeba gingivalis*, *Iodamoeba butschlii*, and *Balantidium coli*.³⁵

Entamoeba coli is a nonpathogenic species.³⁵ The nucleus of *E. histolytica* may have a large, diffuse, eccentric karyo-

some and coarse, unevenly distributed peripheral chromatin, resembling that of *E. coli* (Figs 8.39 & 8.40). Although the two species often can be differentiated in iodine stained preparations,³⁶ a permanent stained smear is necessary for confirmation. The peripheral chromatin of *E. coli* occasionally may appear as a solid dark ring of material. The nucleus of *E. coli* may sometimes contain a central karyosome and uniform peripheral chromatin like that of *E. histolytica*. Immature cysts of *E. coli* containing four or fewer nuclei may be extremely difficult to distinguish from *E. histolytica*, as cyst nuclei frequently have a central karyosome and uniformly distributed peripheral chromatin.

Entamoeba polecki is usually considered nonpathogenic but may cause loose stools or diarrhea.³⁵ Differentiating trophozoites from those of *E. histolytica* may be difficult. Size ranges overlap, and the nucleus of *E. polecki* resembles that of *E. histolytica*, although its peripheral chromatin tends to be more delicate than that of *E. histolytica* (Figs 8.41 & 8.42). Although cysts of *E. polecki* closely resemble the uninucleate cysts of *E. histolytica*, the presence of uninucleate cysts alone should suggest *E. polecki*. A large glycogen vacuole is seldom seen in *E. polecki*. Chromatoid bodies are usually more numerous and pleomorphic in *E. polecki* than in *E. histolytica*.

Endolimax nana is a nonpathogenic protozoon that inhabits the colon and is frequently confused with other small amebae.³⁵ The karyosome of *E. nana* is larger than that of *E. histolytica* (Figs 8.43 & 8.44).

Nonpathogenic *E. hartmanni* was once considered to

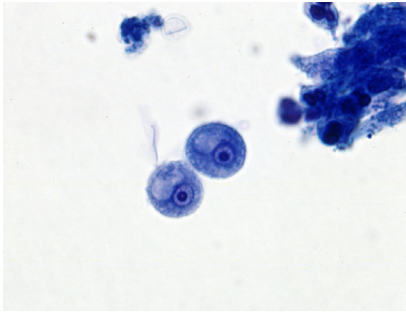


Figure 8.47
Two *Iodamoeba butschlii* trophozoites in fecal smear with large nuclei, large karyosome, and large vacuole, PAP x580

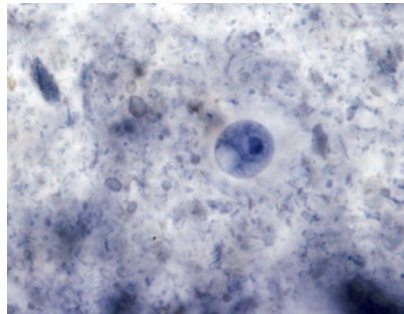


Figure 8.48
Iodamoeba butschlii cyst (12µm diameter) in fecal smear with karyosome and vacuole. Trichrome x840

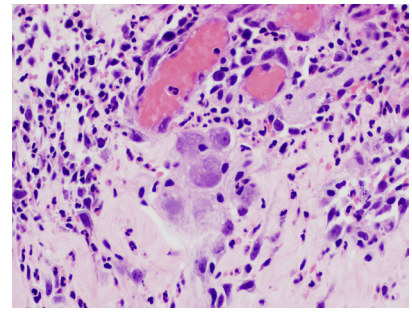


Figure 8.49
Ganglion cells in wall of colon lacks karyosomes of amoeba. H&E x130

be the small race of *E. histolytica*, because of its similar morphology.³⁵ There is some difficulty distinguishing them because the size ranges of the trophozoites and cysts of the two species overlap. The karyosome of *E. hartmanni* usually is smaller and more compact than that of *E. histolytica*, and *E. hartmanni* generally stains more delicately than *E. histolytica* (Figs 8.45 & 8.46).

Entamoeba gingivalis is a nonpathogenic amoeba that occurs in the oral cavity and lacks a cyst stage.³⁵ The nucleus of *E. gingivalis* is similar in morphology to that of *E. histolytica*, having a small central karyosome often with delicate chromatin strands extending to the nuclear membrane, which bears fine peripheral chromatin. The cytoplasm often contains ingested leukocytes in varying stages of digestion, bacteria and other detritus but only rarely erythrocytes. Trophozoites of *E. gingivalis* can be found in scrapings from gum tissues, especially from patients with pyorrhea alveolaris. Since *E. histolytica* trophozoites are rarely found in the sputum of patients with pulmonary abscess, it is necessary to be aware of the potential presence of *E. gingivalis* in sputum. There have been rare reports of *E. gingivalis* in vaginal and cervical smears from women with intrauterine contraceptive devices.³⁷

The cyst stage of non pathogenic *I. butschlii* contains a distinct mass of glycogen in the cytoplasm.³⁵ Occasionally glycogen may occur as a discrete mass in young cysts of *E. histolytica*; however, the two can be distinguished by nuclear structure (Figs 8.47 & 8.48).

Balantidium coli, which may cause identical colonic lesions, is discussed in Chapter 15. This ciliated protozoon is several times larger than *E. histolytica* and has a distinctive shape.

The differential diagnosis of amoebae in tissue sections includes host cells such as histiocytes and ganglion cells (Fig 8.49). Features that distinguish trophozoites in tissue sections include their sharp cellular outline from the surrounding host cells and the round nucleus with a central karyosome. Macrophages and ganglion cells tend to be less sharply demarcated and have oval nuclei.

Methods of detection of *E. histolytica*-specific antigen

in stool or antiamebic antibodies in serum may be more sensitive than microscopy.^{11,12,18,38-41} ELISA for detection of fecal lectin antigen is more sensitive method than culture, although antigens are denatured by fixation, limiting testing to fresh or frozen samples.^{5,42} Serum antiamebic antibodies are present in 70 to greater than 90% of patients with amebic colitis and 70 to 80% of patients with amebic liver abscess.¹⁶ False-negative serologic tests can occur in the first 7 to 10 days of infection, and serologic tests remain positive for years after infection. A combination of serologic tests with detection of the parasite by antigen detection or PCR may be the best approach, although PCR techniques remain impractical in many developing countries.^{5,43,44}

Occasionally, aspiration of a liver abscess is required to rule out bacterial abscess.¹⁶ Amoebae are seen in the abscess fluid in a minority of patients. Less than half of patients with amebic liver abscess have parasites detected in their stool by antigen detection. In rare cases of pulmonary amebiasis, amoebae are found in aspirated pus or expectorated sputum.

Treatment and Prevention

Asymptomatic noninvasive infection should be treated with paromomycin because of its potential to progress to invasive disease.^{11,45,46} Acute colitis should be treated with a nitroimidazole for trophozoites, followed by a luminal agent for cysts. Although approximately 90% of patients with mild to moderate amebic dysentery respond to nitroimidazole therapy, parasites persist in the intestine in as many as 40 to 60%. Therefore, nitroimidazole treatment should be followed with a luminal agent (paromomycin, iodoquinol or diloxanide furoate) to eradicate colonization.⁴⁷⁻⁴⁹ Metronidazole (a nitroimidazole) and paromomycin should not be given at the same time, since diarrhea, a common side effect of paromomycin, may make it difficult to assess the patient's response to therapy. In rare cases of fulminant amebic colitis, it is prudent to add broad-spectrum antibiotics to treat intestinal bacteria that may spill into the peritoneum. Surgical intervention is occasionally required for acute ab-

domen, gastrointestinal bleeding, or toxic megacolon.

At one time, amoebic liver abscesses were almost always fatal, but now even large abscesses can be cured by medical therapy.^{1,50} Nitroimidazoles, particularly metronidazole (Flagyl), are the mainstay of therapy for invasive amebiasis. Nitroimidazoles with longer half-lives (tinidazole, secnidazole, and ornidazole) are better tolerated and allow shorter periods of treatment. Chloroquine is an alternative treatment but is associated with higher relapse rates.⁴⁶ Bacterial infection of amebic liver abscess occasionally occurs spontaneously or as a complication of aspiration; therefore, it is reasonable to use antibiotics in the absence of a prompt response to nitroimidazole therapy.⁴⁶

Imaging-guided percutaneous needle aspiration and catheter drainage of amebic liver abscesses have replaced surgical intervention.⁵¹ Such therapeutic aspiration should be considered in patients in whom pyogenic abscess has been ruled out and in whom there is no response to treatment in three to five days or in those at risk for rupture or pericardial spread.⁴⁶ Abscess cavities greater than 5 cm in diameter or in the left lobe are at a higher risk of rupture.

Amebiasis theoretically could be eradicated. Because humans and primates are the only epidemiologically significant reservoirs, herd immunity in humans could interrupt the fecal-oral transmission cycle.^{11,52} Potentially, a vaccine could be highly protective.^{53,54} Humans acquire partial natural immunity following intestinal infection indicating that a vaccine could stimulate an effective immune response. Improved sanitation could eradicate cyst carriage from a population.⁴⁶ Travelers to endemic areas should avoid eating unpeeled fruits and vegetables and should drink bottled or iodine-disinfected water.

Free-living Amebas (see also Topic 9)

Of the four free-living amebas that are medically important, *Acanthamoeba* sp, *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*, only *Acanthamoeba* and *Balamuthia* produce significant disease outside of the CNS or cornea.⁵⁵ Both *Acanthamoeba* and *Balamuthia* cause infections of the lungs and skin.

In immunocompromised hosts *Acanthamoeba* provokes cutaneous lesions such as disseminated nodules,^{56,57} pustules, and ulcerations (Fig 8.50). Trophozoites and cysts are numerous (Fig 8.51).⁵⁸ Besides skin, *Acanthamoeba* involves the soft palate (Figs 8.52 & 8.53), lung (Figs 8.54 to 8.56), sinuses (Figs 8.57 & 8.58), liver and bone⁵⁹ and abdominal organs including kidney.⁶⁰

Diagnosis follows demonstration of cysts and trophozoites (30 μ m diameter) in hematoxylin and eosin stained histologic sections often in the dermal-hypodermal junction within polymorphous inflammatory granulomas associated with ischemic necrosis.⁵⁸ A polymerase chain reaction (PCR) assay specific for *Acanthamoeba* has been reported

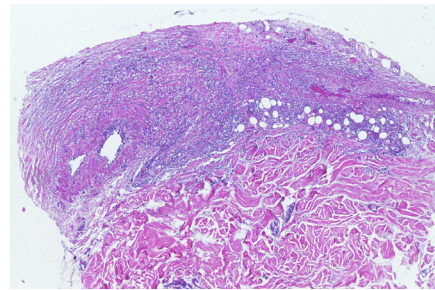


Figure 8.50
Acanthamoeba infection producing necrosis and inflammation in subcutis of an AIDS patient. H&E x19

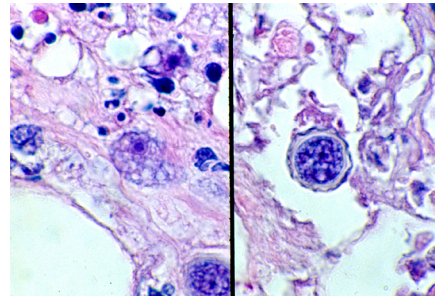


Figure 8.51
Side-by-side comparison of *Acanthamoeba* trophozoite (left) and cyst (right) in subcutis of patient in Fig 8.50. H&E x560

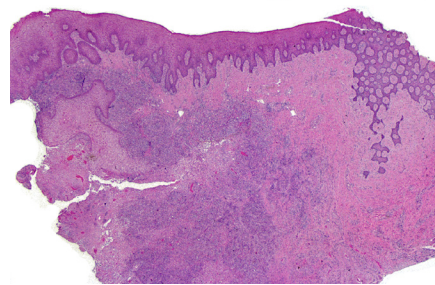


Figure 8.52
Acanthamoeba infection producing suppurative and granulomas in soft palate. H&E x8

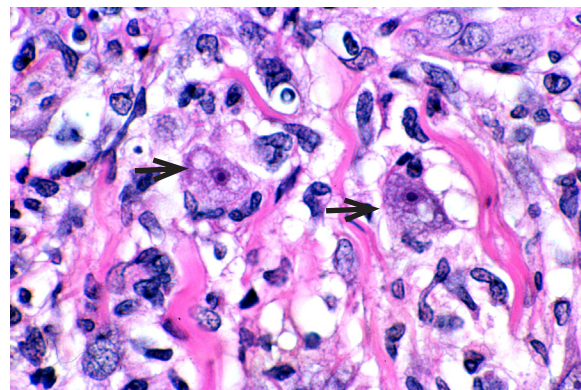


Figure 8.53
Two *Acanthamoeba* trophozoites (arrows) with large karyosomes in soft palate. H&E x550

positive from formalin-fixed paraffin embedded tissue.⁵⁹

Recommended treatments are pentamidine, itraconazole and flucytosine. Due to the morbidity and mortality of *Acanthamoeba* infection optimal therapy must be defined.⁵⁸

Patients with *Balamuthia* infection may present with lesions of the skin, sinus cavities, or middle ear. Skin lesions are painless, may appear as plaques from one to several centimeters wide and are generally single. Lesions appear most commonly in the centre of the face, less commonly on the trunk, and hands and feet.⁵⁵

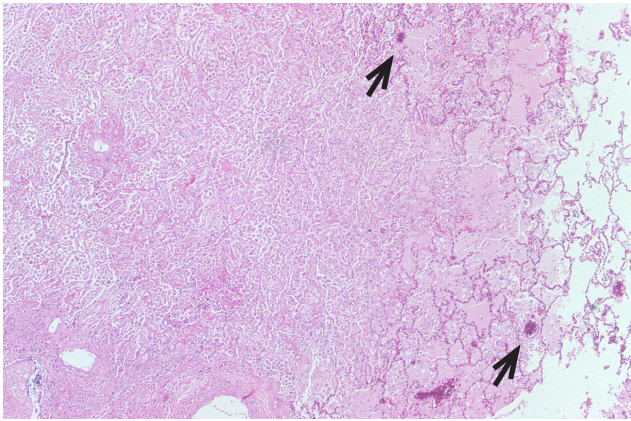


Figure 8.54
Acanthamoeba (arrows) infection producing necrosis in lung in an AIDS patient. H&E x24

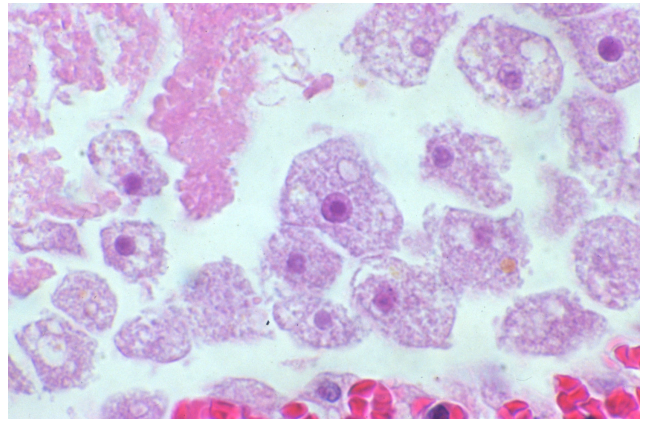


Figure 8.55
Acanthamoeba trophozoites in lung of patient in Fig 8.54. H&E x600

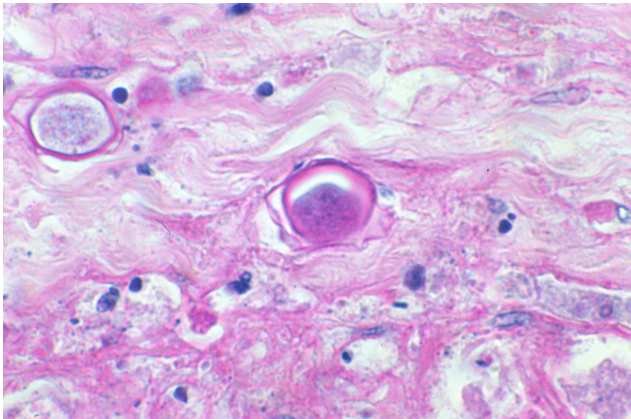


Figure 8.56
Acanthamoeba cyst with double membrane in lung of patient in Fig 8.54. PAS x600

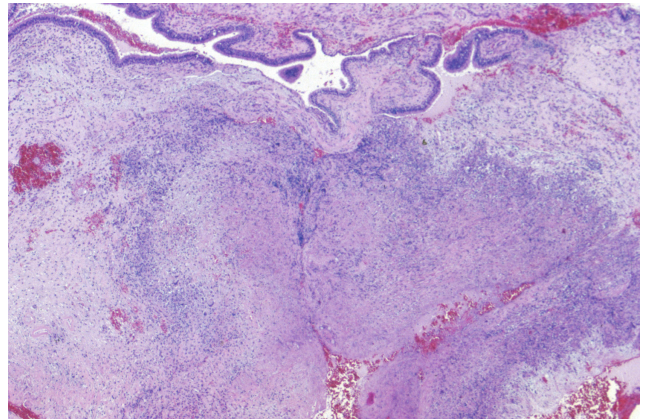


Figure 8.57
Maxillary sinusitis of AIDS patient in Fig 8.54. H&E x24

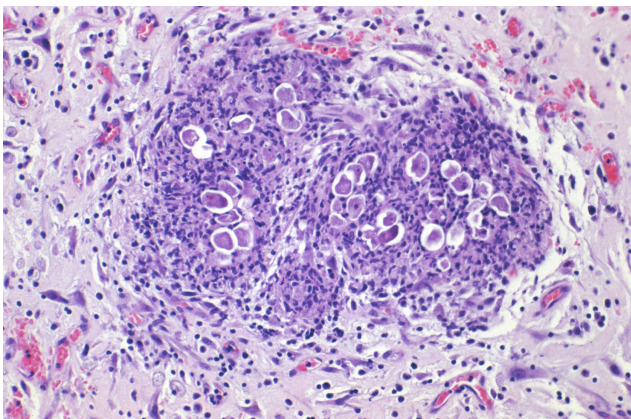


Figure 8.58
Acanthamoeba trophozoites in granuloma in maxillary sinus of patient in Fig 8.54. H&E x145

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Figure 8.15

Contributed by Frank O. Raasch

Figure 8.16

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Figure 8.17

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Figure 8.34

Contributed by R. Elson-Dew